REMARKS

Claims 1-40 are currently pending. Claims 6, 10-13, 21, 25-28, 33 and 37-40 have been withdrawn without prejudice to their rejoinder in this application or prosecution in another application.

I. The Claims Are Definite

The Examiner has rejected claims 1-5, 7-9, 14-20, 22-24, 29-32 and 34-36 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner contends that the phrase "the individual's endogenous protein" recited in the claims has no antecedent basis. The Examiner further alleges that there is no nexus between the "recombinant protein" and "the individual's endogenous protein."

Applicant respectfully disagrees with the Examiner. During the Examiner interviews on September 11 and September 13, 2007, the Examiner informed Applicant that the phrase "the individual's endogenous protein" recited in the claims was indefinite. In the Supplemental Amendment filed on September 17, 2007, Applicant addressed the Examiner's allegation that the claims were indefinite, but in the pending Office Action, the Examiner makes no reference to Applicant's claim amendments or arguments. Thus, it appears that Applicant's amendments and arguments were not considered by the Examiner.

As described in the September 17, 2007 response, Applicant has amended the claims to recite a method of improving gene therapy by increasing the level of expression of a recombinant protein corresponding to an individual's endogenous protein. Accordingly, the nexus between

the recombinant protein and the individual's endogenous protein is specified and the claim is definite.

As stated on page 8, lines 20-24 of the specification:

> "[G]ene therapy" refers to a method of changing the expression of an endogenous gene by exogenous administration of a gene. . . by introducing a functional gene corresponding to the defective or missing gene into somatic or stem cells of an individual in need.

The invention is directed to a method of treating protein deficiencies by enhancing gene therapy with an active site-specific chaperone (ASSC) (*see* page 1, lines 13-14 of the specification). The gene introduced exogenously via a gene therapy vector enables the cells of a treated individual to express a functional protein encoded by the vector. Prior to administration of the gene therapy vector, the individual's endogenous version of the protein was deficient due to, for example:

> disease or as a side effect of a treatment for a disease (e.g. chemotherapy) or as a result of nutritional insufficiency . . . [or] from damage to a tissue or organ resulting from primary or secondary disorders. For example, damaged pancreatic tissue or pancreatitis, is caused by alcoholism [which] results in a deficiency in pancreatic enzymes necessary for digestion."

See page 1, lines 30-32; and page 19, lines 15-18 of the specification. Gene therapy is a treatment option when the protein deficiency results in a pathological condition (*see* page 9, lines 24-29 of the specification). The method of the claimed invention therefore improves gene therapy by increasing the level of functional protein encoded by a gene therapy vector to a level that may, for example, achieve therapeutic benefits, wherein the cell, without the benefit of the introduced vector, did not express a sufficient level of its endogenous protein to maintain normal wild-type activity levels. Applicant asserts that the claims are not indefinite, and request that the rejection be withdrawn.

II. Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32 and 34-36 under 35 U.S.C. § 103(a) as obvious over Yew et al. (U.S. Patent No. 6,066,626) in view of Fan et al. (U.S. Patent No. 6,274,597) and Handa et al. (Dermatology 200:262-265, 2000). The Examiner contends that Yew et al. describes the administration of a biologically active alpha-galactosidase A to patients with Fabry's disease, while Fan et al. discloses methods of increasing the activity of a mutant alpha-galactosidase A in a mammalian cell by administering the chaperone 1-deoxygalactonojirimycin. The Examiner alleges that Handa et al. discloses a patient exhibiting heterozygous female Fabry's disease without a detectable mutation in the alpha-galactosidase A gene. According to the Examiner, the claims encompass methods in which the alpha-galactosidase A deficiency is due to a mutation in a protein other than alpha-galactosidase A, for example, a mutation in an endogenous chaperone protein that is required for proper alpha-galactosidase A folding. Thus, the Examiner states that it would have been obvious to combine the gene therapy of Yew et al. with the chaperone therapy of Fan et al., rendering the claims obvious.

The Examiner has also rejected claim 18 under 35 U.S.C. § 103(a) as obvious over Yew et al., Fan et al. and Handa et al. in view of Hendricks et al. (Blood 96(11 part 1): 845a, 2000). As described above, the Examiner states that Yew et al., Fan et al. and Handa et al. describe methods of increasing the level of expression of alpha-galactosidase A in an individual by administering an alpha-galactosidase A expression vector along with 1-deoxygalactonojirimycin to the individual, wherein the individual does not express a mutant alpha-galactosidase A. According to the Examiner, Hendricks et al. discloses that human mesenchymal stem cells may

be used as the vector to deliver gene therapy constructs to an organism. Thus, the Examiner alleges that the collective teaching of the cited references renders the claims obvious.

Applicant respectfully disagrees. Applicant asserts that the claims are not obvious over the cited references. The present clams are directed to a method of improving gene therapy in an individual whose endogenous protein is not a mutant protein that is deficient due to defective folding or processing in the endoplasmic reticulum. Applicants submit that there would be no motivation or expectation of successfully utilizing chaperone therapy as described by Fan et al. with the gene therapy of Yew et al. As stated by the Examiner in the Final Office Action issued October 4, 2006:

> one of skill in the art understands that chaperone therapy is ***only applicable*** to situations in which a mutant protein can be refolded and would act accordingly. . .

See page 11, lines 8-10 of the October 4, 2006, Final Office Action (emphasis added). Conformational disorders result from "mutations that alter protein folding and retardation of the mutant protein in the ER" (page 14, lines 25-26 of the specification). Conformational mutant phenotypes do not result because the proteins are expressed at an insufficient level, but because once expressed, the proteins adopt an inactive conformation, triggering their degradation and preventing the enzymes from interacting with their substrates.

Additionally, Fan et al. discloses that chaperones are useful for treating Fabry patients whose alpha-galactosidase A is mutant and improperly folded:

> a compound **which is able to induce a proper conformation in [a] mutant enzyme** may serve as an enhancer for the enzyme. The present inventors have unexpectedly found that strong competitive inhibitors for alpha-Gal A at low concentrations enhance the **mutant enzyme** activity in cells . . . According to the present invention, a strategy of administrating an alpha-Gal A inhibitor should prove to be an effective treatment for Fabry

> patients whose **mutation** occurs at the site other than catalytic center . . .

See Fan et al. column 2, lines 2-7 and column 9, lines 53-57 (emphasis added). A skilled artisan absent benefit of the present invention would not have used chaperone therapy under the circumstances disclosed by Handa et al., wherein the gene encoding the disclosed alpha-galactosidase A contained *no detectable mutation*, such as "partial gene rearrangements, splice junction defects, and point mutations" (*see* page 264, third column, first full paragraph of Handa et al.). Based on Fan et al., which is directed to mutant alpha-galactosidase A that is not in a proper conformation, the skilled artisan would not have elected chaperone therapy as a therapeutic option with a reasonable expectation of successfully treating Handa's subject.

The present claims are directed to methods of improving gene therapy in individuals whose protein deficiency is not due to defective folding or processing in the endoplasmic reticulum. Pharmacological chaperone-based therapy would not be expected to have a meaningful effect based on the art cited by the Examiner. Instead, the expression-enhancing effects of pharmacological chaperones are disclosed only in the context of misfolded proteins. Therefore, the presently pending claims are not rendered obvious by Yew et al., Fan et al., and/or Handa et al.

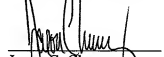
Hendricks et al. discloses that human mesenchymal stem cells may be used as the vector to deliver gene therapy constructs to an organism. Hendricks et al. provides no further guidance to the skilled artisan in practicing the claimed invention, and thus, does not rescue the above-described deficiencies of Yew et al., Fan et al. and Handa et al. The collective teaching of the cited references provides a skilled artisan with no expectation of successfully practicing the claimed invention, and thus do not render the claims obvious. Applicant respectfully requests that the rejection be withdrawn.

III. Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Jason C. Chumney
Patent Office Reg. No. 54,781

Attorneys for Applicants
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, NY 10112-4498
(212) 408-2500